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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/297,181	04/26/1999	LAURENT BRACCO	ST96030-US	9384

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1633	15

DATE MAILED: 11/23/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/297,181 .	BRACCO ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-54* is/are pending in the application.

4a) Of the above claim(s) *45,46 and 48-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-44 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 08/28/01 have been fully considered but is found unpersuasive for the reasons of record as set forth in the earlier office action (Paper No.11, 02/28/01).

This application contains claims 45-46 and 48-54 drawn to an invention nonelected with traverse in Paper No. 10. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 28-54 are pending. Claims 45-46 and 48-54 are withdrawn from further consideration. Claims 28-39, 40-44 and 47 are examined in this office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 28-39 and 40-44 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of restoring p53 transactivation activity in an **isolated cell** (HT29) containing the p53 mutant (His273) by introducing into the cell a nucleic acid encoding single chain antibody (ScFVs: D3M & 421) which bind to mutated P53 protein, does not reasonably provide enablement for the method as claimed in any and all cells in a host **(in-vivo)** using all viral or non-viral vectors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention

commensurate in scope with these claims for the same reasons of record as set forth in the official action mailed on 02/28/01.

Claim 47 stand under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, **to make and/or use** the invention, for the same reasons of record as set forth in the official action mailed on 02/28/01.

The claims 28-39 and 40-44 are drawn to a method of method of restoring p53 transactivation activity in a cell (in-vivo or in-vitro) containing the mutated p53 protein by introducing into the cell a nucleic acid encoding single chain antibody (ScFvs) which bind to mutated P53 protein. The claims are further drawn to the method wherein the ScFvs binds to epitope present in the C-terminal region of p53. The claims are drawn to viral and/or chemical or biochemical vectors wherein the nucleic acid encoding ScFvs is the part of the vector. The claims are further drawn to the method wherein the mutated p53 protein is devoid of tumor-suppressing activity. In addition claim 47 is drawn to a method of treating hyper-proliferative disorder involving mutated p53 protein by administering to a patient a nucleic acid encoding ScFvs which binds to mutated p53 protein and restore transactivation of the p53 protein.

The specification as filed teaches nucleotide sequences encoding the single chain antibody which binds to p53 (ScFv421, SEQ ID NO:1) or p53 mutant H273 (D3M, SEQ ID NO3), see page 29, example-2. The specification further teaches that single chain antibodies 421 and D3M restores the DNA binding function of the in active mutant Trp248 (page 39, example-6, fig-6). The specification further teaches the lipofactamine mediated transfection of a plasmid vector encoding the ScFVs into H1299 tumor cell line, and the expression of the gene product (page 39, example-7, fig.7). In addition the specification teaches the transient transfection of HT29 tumor cell line with plasmid vector encoding D3M and 421 ScFVs (page 39, example-8). The specification further

teaches that the D3M and 421 ScFVs are able to increase transcriptional activity of endogenous mutant His273 in HT29 cells **in-vitro** (page 40 line 18-20, fig-9).

The applicant argues that the specification is enabled for the invention as claimed and the office bears the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention (response: page 3, ¶2). The applicant further argues there is simply no reason in law or logic for requiring applicants to demonstrate that every possible single-chain antibody works for the prevention of hyperproliferation in every possible cell. The specification needs not to contain any example at all if one skill in the art will be able to practice without undue experimentation (response: page 4, ¶2). Similarly, in response to the rejection of claim 47, the applicant argues that there is simply no reason in law or logic for requiring applicants to demonstrate that every possible single-chain antibody works for the prevention of hyperproliferation in every possible cell (response: page 5, ¶2). The applicant further argues that the specification discloses examples in which different tumor cell lines (H358, H1299 and HT29) were transfected with nucleic acid encoding ScFV and showed restoration of p53 transcriprional activity (response: page 5, ¶2). The specification teaches how make various kinds of vectors and how to introduce ScFV into cell to effect the desired response (response: page 6, ¶1). The applicant further argues that reliance on the state of cancer gene therapy in a clinical setting is misplaced as the cited article merely demonstrate the absence of satisfactory results in using gene therapy in cancer cure (response: page 6, ¶2-3). The applicant concluded that one skill in the art would not only be enabled to make and use the applicants invention from the disclosure but also would expect that the method would be useful in treating hyperproliferative disorders involving mutated p53 (response: page 7, ¶2)

However, this is found unpersuasive because the applicant fails to consider that in order to exercise the invention as claimed one would have to introduce into the cell a nucleic acid encoding the single chain antibody, which binds to the mutated p53 protein wherein the single chain antibody restores the transactivation activity of the mutated p53 protein. The applicant fails to consider the earlier office action in it entirety, which

clearly states that the gene based delivery of a therapeutic polypeptide and the treatment of cancer is highly unpredictable wherein the expectation of success is low (Rosenberg et al, Science 287:1751, 2000, Verma, Mol. Ther. 1: 493, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997, Touchette, Nat. Med. 2(1) 7-8, 1996). None of the human studies to date has shown definite efficacy, despite more than 300 protocols involving 3000 patients since September 1990 (Anderson page 25 col.1 para.1). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. The Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success (Touchette page 7, col.1 para. 2; page 8, col.2 para 1-4). The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contributes to a genetic disease along with the pathogenesis of the disease. (Touchette, page 7, col.3, para.3). In instant case, mutation in p53 protein reduces sequence-specific DNA-binding activity, but more refined molecular characterization have shown that the p53 mutants can be divided into at least three distinct subclasses with respect to tetramerization, conformatinal modulation and intrensic-core domain folding. Therefore, to reactive the function of any p53 mutant in cancer cells a complete understanding of structural and functional properties of all p53 mutants is required (Hupp et al, Biochem. J. 352:1-17, 2000, page 7, col.2, para. 2, fig-3).

The earlier office action clearly states that it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors (Verma et al, see page 239 col.3 par.2, page 242, table-2). Although the retroviral vectors are the vectors of choice, they require target cells to be in cycling state for the successful delivery of gene of interest. On the other hand vector comprising DNA viruses and liposome coated DNA have been used to transduce non dividing cells but this results in a transient expression due to non-integration of transgenes in host cells (Verma

et al page 242, table-2). In addition, the use of adenoviral and adeno associated viral vector is also problematic because these vectors elicits considerable immune response in vivo, which affects the sustained expression of the transduced genes (Verma et al, page 241, col.1, par.3; col.3, par.1). Furthermore, in vitro gene transfer studies are not predictive of in vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in vivo environment. In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacle to overcome. The viral particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets (Anderson WF, page 25 col.2, para.4).

In addition, the treatment of a cancer is considered highly unpredictable because various genetic and etiological factors govern the development of the cancer. The carcinogenesis is a progressive disorganization and there is a loss of proliferation controls, increased aneusomy and heterogeneity which leaves limited reliable molecular targets for an intervention therapy (Kelloff et al, Eur. J. Cancer. 35(14):2031-2035, 1999, page 2032, col.2 para.3; page 2034, table-1). Furthermore, the tumors are heterogeneous in respect that they differ in genetic mutations, expression of oncogenes, immunogeneicity and response to environmental changes (Gomez-Navarro et al, Eur. J. Cancer. 35(6);867-885, 1999, page 868, table-1). For example, multiple genetic defects are responsible for the development of breast, lung and colon cancers which renders the cancer gene therapy highly unpredictable (Mastrangelo et al, Semin. in Oncology. 23(1): 4-21, 1996, page 5 col.2, para.3; page 6, table-1; page 8, table-2; page 9 col.1 para. 2; page 19, col.1 para.2). The cancer therapy clearly demands molecular, phenotypic and functional characterization of a particular tumor type that proves amenable to induce cancer amelioration in vivo. Although, mutations in p53 protein reduces sequence-specific DNA-binding activity, more refined molecular characterization have shown that the p53 mutants can be divided into at least three distinct subclasses with respect to tetramerization, conformatinal modulation and intrensic-core domain folding. Therefore, to reactive the function of any p53 mutant in cancer cells a complete understanding of

structural and functional properties of all p53 mutants is required (Hupp et al, Biochem. J. 352:1-17, 2000, page 7, col.2, para. 2, fig-3).

Considering the unpredictability in cancer gene therapy art i) the specification fails to disclose all single chain antibodies that bind to all p53 mutants and restore the p53 transactivation. ii) The specificaition fails to disclose that besides p53-His273 the D3M and 421 ScFVs are able to restore the transactivation of p53-W248 and p53-G281 mutants. iii) The specification fails to disclose the restoration of p53 transactivation in any cell in-vivo by administering any and all viral or non-viral vectors encoding any ScFVs. iv) In addition, the specification fails to disclose the treatment of any and all hyperproliferative disorders involving any and all p53 mutants by administering a patient a nucleic acid encoding ScFVs which bind to all p53 mutants.

It is noted that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991). In instant case the scope of invention as claimed encompass a method of restoring p53 transactivation activity in a cell (in-vivo or vitro) contain a a mutated p53 protein (any and all mutants) by introducing into the (viral or non-viral vectors via systemic or local administration) a single chain antibody which bind to the mutant p53. At best the specification only teaches transient transfection of nucleotide sequences encoding the single chain antibody D3M and 421 ScFVs increases the transcriptional activity of p53 mutant His273 in HT29 cells **in-vitro**. The instant specification does not enable one skill in the art to commensurate in scope with instant claims because the specification fails to meet the enablement requirement as set forth in the first paragraph of 35 U.S.C. 112, which clearly states:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention"

Thus, in view of lack of specific guidance in the specification, the skilled artesian at the time of filing would be unable to use the invention as claimed, without an excessive and undue amount of experimentation. The quantity of experimentation required would include making and functional characterization of any and all ScFVs binding to any and all p53 mutants. The experimentation required would further include making any and all viral and/or non-viral encoding the characterized ScFVs. In addition, the experimentation required would also include successful delivery and the expression of nucleotide encoding the ScFVs in vivo and the restoration of transactivation activity of a mutant p53 protein.

Therefore, the burden shifts to applicant to establish that the invention as claimed is enabled to its full scope because the Office has clearly provided sufficient evidence and sound scientific reasoning to rebut applicant's assertion

Claim Rejections - 35 USC § 102

Claims 28-31, 33 and 39 are rejected under 35 U.S.C. 102(a) as being anticipated by Christain et al (Biochem. Biophys. Res. Com. 230:242-246, 1997), for the same reasons of record as set forth in the official action mailed on 02/28/01.

The applicant argues that the cited art does not discuss a single chain antibody in a cell having a mutant p53 protein but teaches a single chain antibody that bins to wild type p53 protein.

However, this is not found persuasive because the cited art clearly teaches ScFV-421 a single chain antibody that recognizes residues 370-378 of p53 protein (page 242, abstract col.1 para.2), which is present between residues 320-393 of p53 (see claim 31). The prior art teaches isolation and cloning of ScFV-421 nucleic acid into pECE vector. The prior art further teaches the transient expression of ScFV-421 in COS-1 cells using lipofecatamin traransfection method (page 243, col.1 para. 2-3). In addition, the prior art

teaches that the antibody Pab-421 binds to the C-terminus of P53 protein and restores the transactivation function of a p53 mutant (page 242, col.1 para.2; page 245, col.1, para.1). The applicant even fails to consider this limitation in the response filed on 08/20/01 page 8 para.1. Thus, the cited art anticipated the invention as claimed.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Deborah Clark can be reached on (703) 305-4051. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Tracey Johnson, whose telephone number is (703) 308-0377.

If the claims are amended canceled and/or added the applicants are required to follow Amendment Practice under 37 CFR § 1.121 *(http://www.uspto.gov)* and A CLEAN COPY OF ALL PENDING CLAIMS IS REQUESTED to facilitate further examination.

SUMESH KAUSHAL
PATENT EXAMINER

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER